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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/576,785	04/21/2006	Tao Cheng	060230PCTUS	5925

26285 7590 05/01/2009

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EXAMINER	
FORD, ALLISON M	
ART UNIT	PAPER NUMBER
1651	
MAIL DATE	DELIVERY MODE
05/01/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/576,785	CHENG, TAO	
	Examiner	Art Unit	
	ALLISON M. FORD	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 January 2009 and 28 April 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,6-8 and 23-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,6-8 and 23-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 April 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' responses of 1/23/2009 and 4/28/2009 have been received and entered into the application file. Claims 1 and 6 have been amended; claims 4, 5 and 9-22 have been cancelled; new claims 23-28 have been added.

All arguments have been fully considered, and will be addressed below, as appropriate. Rejections/objections not repeated herein have been withdrawn.

Priority

The instant application is a national stage entry under 35 USC 371, of international application PCT/US04/35220, filed 10/25/2004. Acknowledgement is further made of the international application claiming priority to US provisional applications 60/514,329, filed 10/23/2003, and 60/620,154, filed 10/19/2004.

Specification

The amendment to the specification, a corrected version being received in the supplemental response of 4/28/2009, has been entered.

The specification is objected to, however, as failing to contain a reference to each of the drawing figures as required by 37 CFR 1.74. Specifically the "Brief Description of the Figures" at pages 4-6 of the specification is incomplete with respect to the description of Figures 1-4, as there are multiple figures contained within each of Figures 1-4 (1a, 1b; 2a, 2b, 2c; 3a, 3b, 3c, 3d; 4a, 4b), reference should be made to each individual figure. See MPEP 608.01(f).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Applicants have traversed the rejection under 35 USC 112, first paragraph, as lacking written description, on the grounds that the amended claims are now limited to a method of controlling self-renewal of stem cells by reducing intracellular levels of p18 through use of siRNA sequences; Applicants have asserted that appropriate siRNA sequences would have been recognized by those of ordinary skill in the art based on the fact that the sequence of the p18 gene was known in the art.

In response, Applicants' arguments, in combination with the amendments, are found persuasive. What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. See *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d at 1384, 231 USPQ at 94. See also *Capon v. Eshhar*, 418 F.3d 1349, 1357, 76 USPQ2d 1078, 1085 (Fed. Cir. 2005). The claims, now limited to use of siRNA to reduce p18 level, are considered to be supported, as the sequence of the p18 gene was known in the art (See Guan et al, Genes & Development, 1994), and thus determination of appropriate siRNA sequences targeting that gene would have been conventional to one of ordinary skill in the art. See *Noelle v. Lederman*, 355 F.3d 1343, 1349, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004). The rejection is withdrawn.

Applicants have traversed the rejection under 35 USC 112, first paragraph, as lacking enablement, on the grounds that the amended claims now clearly set forth method steps which may be carried out to achieve the desired "control of self-renewal," specifically through use of siRNA sequences to reduce the intracellular p18 level. Applicants assert determination of appropriate siRNA sequences was within the skill level of the artisan of ordinary skill, and thus would not constitute undue experimentation. Applicants further assert determination of the level/degree of p18 reduction effective to

reliably promote self-renewal is not necessary, rather the claims only require a reduction in p18 levels to control self-renewal. Finally, Applicants point to Figure 12b, which shows reduction of p18 levels to 20% of that in a wild-type cell (untreated cell) was achieved through use of siRNA.

In response, Applicants' arguments, in combination with the amendments, are found persuasive. As discussed above, because the p18 gene was known, selection of appropriate siRNA sequences for use to reduce the p18 expression level would have been within the skill level of the ordinary artisan. Furthermore, it is conceded that determination of appropriate degrees/levels of p18 expression/suppression necessary to enhance self-renewal of stem cells would be within the skill of the ordinary artisan, and thus would not require undue experimentation. The successful reduction of p18 levels in murine HSCs through use of siRNA, as reported in Fig. 12b, is noted. The rejection is withdrawn. However, a new rejection under 35 USC 112, first paragraph, has been necessitated by the amendment to the claims, and is set forth below:

Claims 1-3, 6-8 and 23-28 are rejected under 35 U.S.C. 112, first paragraph, as failing to provide enablement for the full scope of the claimed invention. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant's specification is found enabling for promoting self-renewal of a population of hematopoietic stem cells (HSCs) by reducing intracellular levels of p18 through use of siRNA sequences delivered to the HSCs

Applicant's specification is not found to be enabling for *controlling* self-renewal of a population of *any* stem cell by reducing intracellular levels of p18 through use of siRNA sequences. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to carry out the method of the invention commensurate in scope with the current claims.

Analysis of whether a particular claim is supported by the disclosure in an application requires a determination of whether that disclosure, when filed, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention without undue or unreasonable experimentation. See *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916). The key word is 'undue,' not experimentation.' " (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all these factors are considered, a sufficient number are discussed below so as to create a prima facie case.

There are two issues to be addressed: first, whether the specification is enabling for the full scope of *controlling* self-renewal of a population of stems cells, as required by claims 1-3 and 6-8; and second whether the specification is enabling for promoting self-renewal of *any and all* stem cells.

With regards to "controlling":

Applicants' claims 1-3 and 6-8 are directed to *controlling* self-renewal of a population of human-compatible stem cells by reducing intracellular p18 levels through use of siRNA sequences (emphasis added). The term 'controlling' comprises both positive and negative control, as well as maintaining at natural equilibrium; thus the claims encompass both promoting self-renewal of the stem cells as well as suppressing self-renewal of the stem cells, or in other words promoting differentiation of the stem cells.

With regards to predictability in the art of controlling stem cell differentiation/self-renewal, it is acknowledged that progress had been made whereby limited control of differentiation fates of both

mesenchymal and hematopoietic stem cells may be achieved (See, e.g. Deans et al, Experimental Hematology, 2000 for a review on mesenchymal stem cells; See, e.g. Nakauchi et al, Annals of the NY Acad Sciences, 2001 for a review on hematopoiesis). However the known methods of controlling differentiation were generally limited to control of wild-type cells. There was no information on how cells treated with siRNA to have reduced p18 levels would respond to similar treatments. There was limited reports on promoting self-renewal of HSCs by reducing p18 levels (See Sherr et al); however, this is only evidence of promoting self-renewal of one type of stem cell.

The specification provides evidence that $p18^{-/-}$ HSCs show increased symmetric cell division compared to wild-type HSCs (See, e.g. Figure 9). Thus, the disclosure is enabling for promoting self-renewal of the HSCs; however, there is no evidence, or even suggestion in the instant application, of means for suppressing self-renewal of the same stem cells. Because reducing the level of intracellular p18 results in increased self-renewal, additional steps or treatments would be necessary to then promote differentiation of the same cells. There is no disclosure of additional steps or treatments which may be carried out to cause the cells with reduced p18 levels to then differentiate. The Examiner acknowledges that the Office does not require the presence of working examples to be present in the disclosure of the invention (see MPEP §2164.02). However, in light of the state of the art which recognizes a high level of unpredictability in the field of controlling differentiation of stem cells, and limited teachings with regards to the role of p18 levels in stem cell self-renewal, the Office would require appropriate disclosure to support methods for fully controlling stem cell self-renewal.

Due to the lack of teachings in the art regarding suppressing self-renewal of stem cells which have been treated to have reduced p18 levels, and the general unpredictability in the area of controlling stem cell differentiation, a large amount of guidance and teachings would be necessary in order to be enabling for the full scope of "controlling" self-renewal of stem cells.

Therefore, due to the sum of all the aforementioned factors, one of ordinary skill in the art, at the time the invention was made, would not expect success carrying out methods of suppressing self-renewal of stem cells by reducing p18 levels through siRNA, which is included in the breadth of the term "controlling self-renewal of stem cells". Thus, the specification is only found to be enabling only for the "promoting self-renewal" aspect of 'controlling'.

With regards to the type of stem cell:

Applicants' claims are directed to controlling (claim 1) or stimulating (claim 23) the self-renewal of a population of human-compatible stem cells by reducing intracellular levels of p18. For the reasons discussed above the specification is only found to be enabling for promoting self-renewal of stem cells, thus the following rejection will focus on other stem cell types which may be successfully *promoted* (stimulated) to self-renew by the instant method.

The current claims encompass all types of stem cells. It is noted that 'human-compatible' is defined in the specification as able to be survivably implanted in a human (See Pg 24, ln 8-14). The definition permits use of immunosuppressants, thus any cell may be considered human compatible, as the human immune system may be completely suppressed to permit survival of the implanted cell. As such, all stem cells are considered 'human-compatible'. Thus the breadth of the current claims includes promoting self-renewal of a population of any type of stem cell, including embryonic stem cells and adult stem cells, including pluripotent stem cells, like mesenchymal stem cells and hematopoietic stem cells, as well as lineage specific stem and progenitor cells, such as neural stem cells, epithelial stem cells, hair follicle progenitor cells, and more.

With regards to predictability in the art in the field of promoting self-renewal of stem cells, in general promoting self-renewal of any adult stem cell was unpredictable, at best (See, e.g. Deans et al, Experimental Hematology, 2000 and. Nakauchi et al, Annals of the NY Acad Sciences, 2001). Yet the

claims more specifically require the increased self-renewal to be achieved by a reduction in intracellular level of p18. Understanding of the role of p18 in cell growth and development was nascent at the time of filing, the p18 gene only being identified in 1994 (Guan et al, Genes & Development, 1994). While p18 was considered to play a role in multiple cell types (See Franklin et al, Genes & Development, 1998), only its role in hematopoietic cells was well understood. Work by Sherr et al identified p18 functions as a 'brake' in the G1→S transition of HSCs (See Sherr et al, col. 4, ln 46-54); thus elimination of the p18 protein resulted in increased proliferation (See Sherr et al, col. 5, ln 11-18). Therefore, the art, like the instant application, supports the role of p18 in hematopoiesis, and specifically that suppression of the p18 results in increased proliferation of HSCs (See Sherr et al, col. 5, ln 11-18). However, at the time the invention was made the role of p18 in non-hematopoietic stem cells was not understood and not fully characterized (See, e.g. Franklin et al), and thus there was a recognized level of unpredictability with regards to the effect of modulation of the p18 levels in other cell types, specifically other stem cell types.

The specification does provide evidence that $p18^{-/-}$ HSCs exhibit increased self-renewal as compared to non-treated cells (See, e.g. Figure 9). The specification further provides evidence that intracellular p18 levels can be reduced in murine and human HSCs (See, e.g. Figure 12b). Therefore, the specification is found enabling for a method of promoting self-renewal of HSCs by reducing the p18 level through siRNA sequences. There are no examples of reduced p18 levels in any other type of stem cell resulting in increased self-renewal. Guidance and teachings provided by the Applicant regarding applicability of the method to non-HSC stem cells is limited to a statement that "[G]iven the non-specific expression of p18 in hematopoietic cells, this approach can also be applied to other stem cells types in the body" (See Spec at Pg. 4, lines 1-2).

Due to the lack of teachings in the art regarding the role of p18 in stem cells beside HSCs, and the recognized unpredictability in the area of controlling stem cell differentiation & self-renewal, a large amount of guidance and teachings would be necessary in order to be enabling for controlling self-renewal

of all stem cell types by reducing intracellular p18 levels; however, as discussed above, the instant specification fails to provide such teaching and guidance. The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Thus, due to the high level of unpredictability in the art, the current specification would have to provide greater amounts of teachings and guidance directed to methods of carrying out the claimed invention. A large amount of undue experimentation would be required to determine the parameters and additional conditions (in addition to reduction of p18 levels) necessary to successfully promote self-renewal of all stem cells, or if such can even be achieved.

Therefore, due to the sum of all the aforementioned factors, one of ordinary skill in the art, at the time the invention was made, would not expect success carrying out the method of promoting self-renewal of any type of stem cell except for HSCs by reducing intracellular p18 levels. Given that the art fails to recognize and Applicant has failed to demonstrate that any species of stem cell, besides HSCs, will exhibit enhanced self-renewal upon reduction of intracellular p18 levels, the skilled artisan would be faced with the impermissible burden of undue experimentation in order to practice the claimed invention on any species of stem cell. Accordingly, claims 1-3, 6-8 and 23-28 are deemed properly rejected.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2, 6, 7, 24, 26 and 27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 2, 7, 24 and 27 each require that the stem cells be 'predominantly undifferentiated stem cells.' Stem cells are functionally defined as having capacity for self-renewal and differentiation (See Cheng, Gene Therapy, 2008, paragraph spanning pages 68-69); thus stem cells are defined as undifferentiated cells. Therefore the limitation in claims 2, 7, 24 and 27 requiring the stem cells to be only *predominantly* undifferentiated stem cells renders the claims indefinite, as such infers that not all the stem cells need to be undifferentiated (in which case they would not be stem cells). Clarification is required. Yet, please note that if the claims are amended to delete the term 'predominantly', so as to require the stem cells *are* undifferentiated stem cells, the claims would be objected to as failing to further limit the parent claim.

In claims 6 and 26, in the step of implanting human-compatible stem cells into a human, it appears the claims should read "implanting the human-compatible stem cells into a human…" Without referencing *the* human-compatible stem cells from claims 1 or 23, respectively, it is unclear how claims 6 and 26 correlate with the method of the parent claims.

Furthermore claims 6 and 26 are rejected for lacking antecedent basis for the limitation "the implanted human stem cells" in the last line of each claim. Neither of claims 6 or 26 limit the stem cells to *human stem cells*, but only human-*compatible* stem cells. Correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Applicants traversed the rejection of record under 35 USC 102(b) on the grounds that Sherr et al does not teach reducing the levels of p18 to control self-renewal, but rather to effect cell proliferation. Applicants assert self-renewal and proliferation, in the context of stem cells, have opposite results, and thus are not similar processes. Furthermore, Applicants assert Sherr et al does not teach use of siRNA, but rather use of antisense oligonucleotides, which is a distinct method.

In response, Applicants' arguments, in combination with the amendments, are persuasive to necessitate removal of the rejection from 35 USC 102(b), as Sherr et al does not teach each and every limitation of the claims. However, a new rejection has been made under 35 USC 103(a), on the grounds that Sherr et al render obvious the claimed invention. Pertinent arguments are addressed within the rejection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 1-3 and 23-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sherr et al (US Patent 6,033,847), in view of Bertrand et al (Biochemical & Biophysical Research Comm, 2002) and further in view of An et al (Human Gene Therapy, 2003) and Walters et al (Antisense and Nucleic Acid Drug Development, 2002).

Sherr et al disclose a method of controlling proliferation of hematopoietic stem cells (HSCs) by reducing p18 levels within the HSCs by blocking expression of the p18 gene through use of antisense oligonucleotides (See Sherr et al col. 5, ln 11-39).

HSCs are considered to read on human-compatible stem cells in accordance with the definition in the instant specification (Pg 24, ln 8-14), which defines "human compatible" to mean able to be survivably implanted in a human. The definition permits use of immunosuppressants, thus any cell may be considered human compatible, as the human immune system may be completely suppressed to permit survival of the implanted cell. HSCs are considered undifferentiated stem cells, as they are, by definition, not terminally differentiated.

Sherr et al do not disclose the source of the treated HSCs, however, Sherr et al does state the p18 gene sequences which are the subject of their disclosure may be of human origin (See Sherr et al, col. 4, ln 55-58); thus the method of Sherr et al is considered to be applicable to human HSCs, as they have identified the human genes.

Sherr et al differs from the instant invention in that they use antisense oligonucleotides, not siRNA molecules to reduce the intracellular levels of p18 within the HSCs. However, it is submitted that one of ordinary skill in the art, at the time the invention was made, would have found it *prima facie* obvious to use either siRNA or antisense oligonucleotides to block expression of the p18 gene in the method of Sherr et al. Antisense oligonucleotides and siRNA molecules were both recognized as effective agents to inhibit gene expression in mammalian cells by degrading targeted messenger RNA, while the mechanisms of action differ, the end result is equivalent (See Bertrand et al, Pg. 1000, col. 1). Both antisense oligonucleotides and siRNA against a specific gene product may be routinely produced by the artisan of ordinary skill when the sequence of the target gene is known, per Applicants submission (See Response Pg 10). In the instant case the sequence of the p18 gene is disclosed in the art, and by Sherr et al, thus appropriate siRNA molecules would have been routinely produced without undue experimentation. Therefore, it would have been obvious to one of ordinary skill in the art to alternatively employ siRNA molecules targeted to the p18 gene sequence, in place of antisense oligonucleotides in the

method of Sherr et al, for the predictable result of reducing p18 expression levels in the intracellular environment., thereby promoting proliferation of the HSCs. It has been held that substitution of one element or technique for another known in the field is considered to be obvious, absent a showing that the result of the substitution yields more than predictable results. See *KSR International Co. v Teleflex Inc* 82 USPQ2d 1385 (US 2007) at page 1395.

It is further noted that siRNA molecules are routinely delivered to cells through lentiviral vectors (See An et al, Pg 1228, "Lentiviral Vector Production") or by electroporation (See Walters et al, Pg 417, col. 2). Selection of either art accepted method for delivery of an siRNA molecule to the HSCs in the method of Sherr et al would therefore have been prima facie obvious to one of ordinary skill in the art, with a reasonable expectation of successfully delivering the siRNA molecule to reduce p18 expression, thereby resulting in increased proliferation of the HSCs.

It is noted that Applicants have argued that Sherr et al only report proliferation of the stem cells, which they assert is distinct from self-renewal; however it is respectfully submitted that *proliferation* is not necessarily *differentiation*. The post-filing date article relied upon in the arguments (Cheng, 2008) differentiates between self-renewal and differentiation/maturation of stem cells, this difference is not disputed; however *proliferation*, by definition, is simply multiplication of parts, and in the filed of cell biology, increased cell number by division. Thus Sherr et al in using the term 'proliferation' does not mean the HSCs are differentiated. Rather, because Sherr et al are causing the same molecular change (reduced level of p18) in the same type of cells (HSCs) as is performed in the methods of the current application, the same results are necessarily yielded: self-renewal of the HSCs, at least to the same extent that can be achieved by the instant method. Thus, the method of Sherr et al, which involves delivery of antisense oligonucleotides to HSCs to reduce intracellular p18 levels, would render obvious the current

method of delivering siRNA sequences to the same cells to reduce intracellular p18 levels, resulting in enhanced self-renewal of the HSCs. Therefore the invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claim 1-3, 6-8 and 23-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sherr et al (US Patent 6,033,847), in view of Bertrand et al (Biochemical & Biophysical Research Comm, 2002) further in view of An et al (Human Gene Therapy, 2003) and Walters et al (Antisense and Nucleic Acid Drug Development, 2002), and further in view of Largman et al (US Patent 5,837,507).

The teachings of Sherr et al, Bertrand et al, An et al and Walters et al are set forth above. When taken as a whole these teachings render obvious the claimed method of promoting self-renewal of HSCs by reducing intracellular p18 levels through use of siRNA sequences.

Sherr et al does not disclose further reintroducing the expanded population of HSCs (resulting from enhanced self-renewal) back into a human. However, it is submitted that transplantation of HSCs, including HSCs which have been modified to have enhanced self-renewal capacity, to human patients for reconstitution of the hematopoietic system was a known therapy in the art (See, e.g. Largman et al, col. 2, ln 66- col. 3, ln 9). The method of Sherr et al results in HSCs with enhanced self-renewal capacity; therefore it would have been *prima facie* obvious to one ordinary skill in the art, at the time the invention was made, to employ the cells of Sherr et al in the known method of hematopoietic reconstitution (See, e.g. Largsman et al) for the predictable result of promoting reconstitution of the hematopoietic system in a human patient in need thereof. Thus, the invention as a whole would have been *prima facie* obvious to the artisan of ordinary skill.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ALLISON M. FORD whose telephone number is (571)272-2936. The examiner can normally be reached on 8:00-6 M-Th.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Allison M. Ford/
Primary Examiner, Art Unit 1651